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Preface

# What's so special about chicken immunology?

What's so special about chickens? Firstly, chickens are not only an invaluable model for studying immunology they also provide the world's main source of meat and will be a key protein source needed to feed the growing human population into the future. Poultry meat production is highly efficient in converting grain feed to protein and does so with less environmental impact (low water and energy use and low greenhouse gas production) compared to other forms of meat production systems (de Verdal et al., 2011). Currently, some 80 billion chickens are hatched each year, producing around 105 million tonnes of meat and 70 million tonnes of eggs (USDA, 2012). One of the greatest threats to the poultry industry is the impact of infectious diseases. Therefore, in order to sustain a safe and healthy supply of poultry, a greater understanding of chicken immunity to pathogens underpins future poultry production.

Furthermore, poultry play an important role in the spread of emerging infectious diseases, such as avian influenza, that can impact on human health. Understanding the host-pathogen relationship has important implications for preventing the transfer of zoonotic pathogens from poultry to humans and for the development of novel treatment strategies. The World Health Organization has warned that the source of the next human flu pandemic is likely to arise from chickens. This point has recently been reinforced by the current outbreak of H7N9 avian influenza in China, prompting warnings that the world is unprepared for a massive virus outbreak. This highlights the importance of controlling this disease in poultry and similarly highlighting the need for a better understanding of the immune response in the chicken to pathogens such as avian influenza.

Studying the immune system of chickens has lead to critical contributions to immunological tenets. The fact that the chicken immune system does things a bit differently, while still being able to mount effective immune responses, speaks to the benefits and knowledge gained from the comparative studies of diverse species. The unique chicken organ, the Bursa of Fabricius, has provided extensive information about B cell development and function. Moreover, the easy accessibility to the chicken embryo has not only aided in our understanding of B cell development, but also T cell maturation in the thymus. Furthermore, the first interferon activity was discovered in the chicken (Isaacs and Lindenmann, 1957). Therefore, off particular relevance to this Special Issue, apart from rodents and humans, arguably the most thoroughly characterised immune system is that of the chicken.

The release of the chicken genome (Wong et al., 2004) has lead to rapid advances in chicken immunology and together with new technologies and reagents has facilitated a better understanding of chicken immune responses to important pathogens that affect both animal and human health. These developments will inform important disease control measures through novel vaccine design, improve animal welfare, and shed light on the susceptibility of poultry to zoonotic diseases impacting human health.

Host responses leading to protection against pathogens are highly complex, involving many aspects of innate and adaptive immunity. Innate immunity is mediated by various subpopulations of innate immune cells through the secretion of soluble factors with diverse functions upon the recognition of the pathogen associated molecular patterns by the host pattern recognition receptor molecules. Adaptive immunity, which is important in conferring protection against subsequent infections, involves many subtypes of T and B lymphocytes that mediate antigen-specific immune responses. This Special Issue covers several areas of chicken immunology, starting with a number of papers that review the current status of innate immunity and describe the key cell types and factors (such as cytokines, interferons and peptides) involved in the innate response.

Recognition of potential pathogenic microbes by the innate immune system is the function of a class of cellular receptors known as pattern-recognition receptors (PRRs), which include Toll-like receptors (TLRs) (Medzhitov et al., 1997). The TLR superfamily represents an evolutionarily conserved signalling system that is a decisive determinant of the innate immune and inflammatory responses. The innate system uses these germ-line encoded receptors to detect evolutionarily conserved microbial proteins, lipids, and nucleic acids on microbes. Microbial product-induced activation leads to the activation of intracellular signalling pathways that initiate microbial killing mechanisms, the production of pro- and/or anti-inflammatory cytokines, and up-regulation of co-stimulatory molecules required for antigen presentation to the acquired immune system. The review by Keestra and colleagues describes that some TLRs are retained in birds and mammals, but others are unique for birds albeit that recognize very similar microbial products.

A number of specialized cell types play key roles in the innate immune response. Natural killer cells use a diverse range of receptors to recognize and destroy virally infected or transformed cells. The review by Straub et al. discusses the recent progress on studying the role of the diverse types of NK cell receptors, with special emphasis on novel families recently identified in the chicken genome. Likewise, heterophils also play an indispensable role in the immune defence of the avian host by using a large repertoire of armaments and signals defend the host and to influence the direction of the immune response. Genovese et al. describe the recent

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advances in our understanding of the avian heterophil, its functions, receptors and signalling, identified antimicrobial products, cytokine and chemokine production, and some of the effects of genetic selection on heterophils and their functional characteristics. Macrophages and dendritic cells also play crucial roles in protection against pathogens. The paper by de Gues et al. discusses how the function of these cells is regulated in the innate immune response to respiratory and intestinal pathogens and provides insights into how these responses may be modulation through the use of nutraceuticals and vaccination.

The prevalence of emerging pathogenic viruses, such as avian influenza, is a serious issue as they pose a constant threat to both the poultry industry and to human health. One approach in the control of viral infections would be to boost the immune response through administration of cytokines or interferons. However, the innate immune response in chickens is poorly characterised, particularly concerning the interferon pathway. The review by Goossens et al. provides an overview of our current understanding of the interferon system of chickens, including the key receptors and interferon-stimulated gene products involved. Correspondingly, Guo et al. reviews the key cytokines involved in the TH-1 immune responses to viruses and explores their potential use in enhancing anti-viral treatment strategies in chickens. They describe how interferon gamma may have the potential to be used as a novel therapeutic to impact infection and alter immunosuppression caused by CAV and potentially other pathogens. A second class of secreted factors, known as host defense peptides (HDPs) are diverse group of small and cationic peptides that are known to be important effector molecules of the innate immune system of vertebrates but have also been found in invertebrates, plants and fungi. Research has showed that these peptides possess many additional functions, including immunomodulation and wound healing. The review by Cuperus and colleagues addresses the current knowledge on the evolution, regulation and biological functions of HDPs of birds and compare the avian peptides to their mammalian counterparts.

Whereas innate responses provide a rapid and broadly defined protection against pathogens, the adaptive immune response provides a somewhat longer term, pathogen-specific immunity. Furthermore, this response provides memory, that is, an ability of the host to mount a strong rapid response to future re-infection by the same pathogen. Regulatory T cells (Murchison et al., 2012) have been described in many species and are identified by their expression of $CD4^{+}CD25^{+}FoxP3^{+}$. Chickens appear to lack the FoxP3 marker, however, thymic $CD4^{+}CD25^{+}$ cells produce high amounts of interleukin (IL)-10 and transforming growth factor-β. Additionally, in chickens Treg suppress the activity and proliferation of several immune cells through both contact-dependent pathways that include cytotoxic T-lymphocyte antigen 4, and lymphocyte-activation gene 3 and contact-independent pathways through immunosuppressive cytokines. Selvaraj et al. reviews the current status of Tregs in chickens and hypothesizes as to how therapy targeted towards alleviating Treg mediated immune suppression can improve host immunity against those persistent pathogens and benefit poultry production.

Since the chicken genome became available, Viertlboeck and colleagues have identified and studied chicken homologues of various immunoregulatory Ig-like receptor families, which cluster on distinct chromosomal regions. In mammals, members of the immunoregulatory Ig-like receptor families facilitate the coordination of the immune response at the cellular level. In their review, current progress on chicken immunoregulatory Ig-like receptor families is described. In addition, new data is presented further characterizing ggTREM-A1 expression at the mRNA and protein level in various cells and tissues of chickens.

Associated with the intensive nature of poultry production, chickens are often susceptible to infection by pathogens that either directly affect the birds themselves or pose a threat to humans (e.g. campylobacter and avian influenza). This may be exacerbated by the fact that birds have a smaller repertoire of immune genes than mammals. Magor and colleagues summarize their studies on antiviral responses to influenza in avian hosts and note key genes present in other species that appear to be missing in chickens. As a result, they speculate that birds may have an impaired ability to detect viruses and intracellular pathogens.

This Special Edition contains a number of reviews that describe immune response mechanisms in chickens involved in providing protection against various protozoan, bacterial and viral pathogens. Coccidiosis is the most economically important protozoan disease in chickens causing a variety of clinical manifestations ranging from inefficient feed utilization, and loss of productivity to mortality. Min et al. describe the role of the IL-17 cytokine family in inflammation and in local defense against invading pathogens including parasites and discuss how better understanding their biological function in avians will be important in developing a new strategy against protection against coccidiosis.

Most studies that have described avian immunity to bacterial infections are based on studies with Salmonella because of its zoonotic nature. Wigley et al. updates the literature on the interactions between the avian host and salmonella infections and describes how new systems approaches will provide a better understanding of the protective immune responses to, not only Salmonella, but other poultry pathogens such as pathogenic *Escherichia coli* and *Clostridium perfringens*.

With regards to viral diseases in chickens, infectious Bursal Disease Virus (IBDV) targets the chicken's immune system in a complex manner by destroying B lymphocytes, attracting T cells and activating macrophages, resulting in immunosuppression. Recent studies have shown that highly virulent forms of IBDV cause high rates of mortality, possibly through the induction of an exacerbated innate immune response, resulting in a cytokine storm. Although satisfactory protection may be provided by the induction of high neutralising antibody titres, interference from maternal antibodies has become a major obstacle in the establishment of vaccine control programs. The review by Ingrao et al. describes how recent progress in the field of avian immunology has allowed a better knowledge of the immune response to IBDV and how recombinant HVT and immune complex vaccines show promising results.

Marek's disease virus (MDV) has been a major concern to poultry production for the past 50 years. The natural route of infection is via the respiratory tract after inhalation of cell-free virus particles, followed by transportation of MDV to lymphoid organs. MDV causes clinical signs such as paralysis and immune suppression. Even though vaccination strategies are in place, the continued emergence of ever increasingly virulent strains remains a major issue. The review by Haq et al. explores the mechanisms of host immunity against MDV and identifies the areas where we need to increase our understanding.

Newcastle disease (ND) remains a constant threat to poultry producers worldwide, in spite of the availability and global employment of ND vaccinations since the 1950s. Immunity is derived from neutralizing antibodies formed against viral hemagglutinin and fusion glycoproteins, which are responsible for attachment and spread of the virus. The review by Kapczynski et al. discusses approaches that allow a more in depth analysis of the innate and cell mediated immune responses, highlighting the importance of a more complete understanding of the global immune response of poultry to NDV in developing new control strategies and intervention programs for the future.

Infectious laryngotracheitis virus (ILTV) causes upper respiratory tract disease in chickens and affects the poultry industries worldwide. The view by Coppo et al. examines the current understandings of innate and adaptive immune responses towards ILTV, as well as the role of ILTV glycoprotein G in modulating the host immune response with the view of developing a new generation of vaccines to enhance control of this disease.

Finally, Stewart et al. discuss how next generation technologies including functional genomics, targeted gene disruption (e.g. zinc finger nucleases and meganucleases), RNA interference and transgenics will be developed and employed as new approaches to poultry immunology research. These technologies can be employed not only for understanding immune responses in poultry, but also the potential for the development of novel disease intervention strategies.

Immunological developments in the chicken, such as the first use of an attenuated vaccine by Pasteur, have lead to benefits for both humans and other animals. Furthermore, important outcomes as a result of researching immunology in the chicken will continue to provide knowledge to not only develop novel approaches to support poultry health but to further extend this knowledge to support human and veterinary medicine. Clearly, the chicken is special and it will continue to be an important aspect of developmental and comparative immunology.

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